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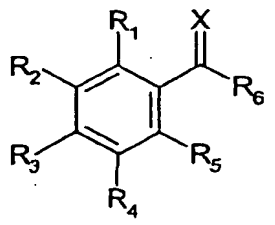
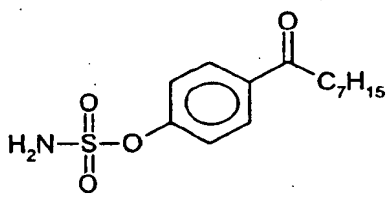
(54) Title: SULPHAMATE COMPOUNDS



(A)



(B)

(57) Abstract: Non-steroidal sulphamate compounds of formula (A), such as (B), which inhibit oestrone sulphatase and dehydroepiandrosterone sulphatase and are thus useful in treating sulphatase-associated conditions such as breast cancer.

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SULPHAMATE COMPOUNDS

Technical Field

The present invention relates to members of a family of non-steroidal compounds which have been found to possess inhibitory activity against the enzyme oestrone sulphatase.

Background Art

Although plasma oestrogen concentrations are found to be similar in women with or without breast cancer, breast tumour levels of oestrone and oestradiol are significantly higher than in normal breast tissue or blood. Synthesis of oestrogens within tumours is thought to make an important contribution to these high levels of the female hormones. Oestrogens are suggested to be the major mitogens involved in promoting the growth of tumours in endocrine-dependent tissues, such as the breast and therefore specific inhibitors of oestrogen biosynthesis are of potential value for the treatment of endocrine-dependent tumours.

Recently, there has been considerable interest in the development of inhibitors of the cytochrome P-450 enzyme aromatase (AR) - a pathway which is responsible for the conversion of androgens into oestrogens, e.g. androstenedione to oestrone.

There is now evidence, however, that the oestrone

sulphatase (EI-STS) pathway [the hydrolysis of oestrone sulphate (2) to oestrone (1) (EIS to El) (see Fig. 1)] is the major source of oestrogen in breast tumours[1,2] as opposed to the AR pathway. This is supported by a modest reduction of plasma oestrogen concentration in postmenopausal women with breast cancer treated by AR inhibitors, such as aminoglutethimide (AG) and 4-hydroxyandrostenedione[3,4,5].

The oestrone sulphatase inhibitors are sulphamate esters, such as oestrone-3-sulphamate (otherwise known as "EMATE").

EMATE (Compound 3: see Figure 1) is a potent EI-STS inhibitor and displays more than 99% inhibition of EI-STS activity in intact MCF-7 cells at 0.1μM concentration. EMATE also inhibits dehydroepiandrosterone sulphatase (DHEA-STS), an enzyme that is believed to have a crucial role in regulating the biosynthesis of the oestrogenic steroid androstenediol[1]. Furthermore, there is now evidence to suggest that androstenediol[1] may be of even greater importance as a promoter of breast tumour growth[6]. Another known inhibitor is COUMATE (Compound 4: see Fig. 1).

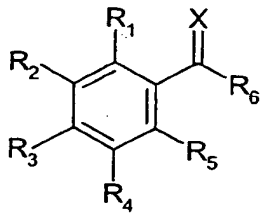
Although potency for the inhibition of E1-STS may have been attained in EMATE, it has been suggested that oestrone may be released during sulphatase inhibition[7] and that EMATE and its analogues may possess oestrogenic activity[8].

Disclosure of Invention

This present invention therefore seeks to provide compounds suitable for the inhibition of E1-STS and/or DHEA-STS. Preferred compounds possess no, or a minimal, oestrogenic effect.

According to a first aspect of the present invention there is provided a non-steroidal sulphamate compound suitable for use as an inhibitor of oestrone sulphatase and/or dehydroepiandrosterone sulphatase wherein the compound has a ring structure wherein the ring mimics the A ring of oestrone.

Preferably the compound is of formula (A):



(A)

wherein R_1-R_5 are independently selected from H, halo, alkyl, nitro, CN, aryl, OH, OR' (where R' is alkyl or aryl), $NR"_2$ (where each R" is independently H, alkyl or aryl) and sulphamate groups, with the proviso that at least one of them is a sulphamate group; X is selected from O, S, NH, NR''' (where R''' is alkyl or aryl), and R_6 is selected from H, alkyl, aryl, alkoxy, aryloxy and $NR"_2$ and/or is a compound of formula (A) wherein one of R_1-R_5 is a sulphamate group and the others are selected so that the compound is a sulphamate ester of a phenol having a

pK_a in the range 7-9.

'Alkyl' encompasses branched, cyclic and straight chain alkyl. It includes substituted alkyl, e.g. aralkyl. Other possible substituents include halo, RCO (R=alkyl or H) and nitro. Alkyl groups may include unsaturation. They may be interrupted by heteroatoms e.g. O, N or S. Alkyl groups are preferably C_{1-13}, more preferably C_{1-9}, especially C_{1-6}.

'Aryl' encompasses substituted aryl. Possible substituents include alkyl, halo, nitro and cyano. 'Aryl' encompasses heteroaryl. Aryl groups are preferably up to C_{15}.

Preferably X is oxygen. The $-C(=X)-R_6$ sidechain is preferably an ester, amide or ketone moiety.

The term "sulphamate" as used herein includes an ester of sulphamic acid, or an ester of an N-substituted derivative of sulphamic acid, or a salt thereof. Thus, the term includes functional groups of the formula: $-O-S(O)(O)-N(R_7)(R_8)$ where R_7 and R_8 are independently selected from H, linear or branched alkyl which may be saturated or unsaturated and/or substituted or non-substituted, aryl, or any other suitable group.

Preferably, at least one of R_7 and R_8 is H. In a preferred embodiment, each of R_7 and R_8 is H.

According to a second aspect of the present invention there is provided a compound of the first aspect for use as a pharmaceutical product.

According to a third aspect of the present invention there is provided the use of a compound of the first aspect for inhibiting oestrone sulphatase

According to a fourth aspect of the present invention there is provided a pharmaceutical composition comprising a compound according to the first aspect; and a pharmaceutically acceptable carrier, excipient or diluent. (Such materials are well-known to those skilled in the art, and are too diverse to be stated here).

According to a fifth aspect of the present invention there is provided the use of a compound of the first aspect in the manufacture of a pharmaceutical product for inhibiting oestrone sulphatase and/or dehydroepiandrosterone sulphatase, e.g. for use in the treatment or prophylaxis of conditions associated with oestrone sulphatase and/or dehydroepiandrosterone sulphatase activity, e.g. endocrine-dependent cancers (particularly breast and prostate cancer); autoimmune diseases; and conditions affecting short and/or long term memory.

Compounds and compositions embodying the invention may be administered to individuals (human or non-human). Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend

on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors.

A compound may be administered alone or in combination with other treatments, either simultaneously or sequentially, dependent upon the condition to be treated.

Pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to the active ingredient, i.e. a compound of formula A, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. topical, subcutaneous, or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other

saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such a gelatin.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable solution, usually aqueous, which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

Preferably one of R_1-R_5 is sulphamate and the others are independently selected from H, alkyl and haloalkyl.

Preferably R_3 is OSO_2NH_2 or other sulphamate group.

Preferably the compound is any one of the compounds shown as Compounds 11-16 in Figure 2, particularly 4-O-sulfamoyl octaphenone or 4-O-sulfamoyl nonophenone, or a variant in which R_1-R_5 include one or more electron withdrawing substituents, e.g. NO_2, CN or halo.

Preferred compounds of the present invention may have little or no oestrogenic activity, in particular, less than EMATE. They can therefore be deemed to be non-oestrogenic compounds.

The term "non-oestrogenic compound" as used herein

means a compound exhibiting no or substantially reduced oestrogenic activity.

The present invention therefore provides non-steroidal compounds which have a reduced oestrogenic activity. In this regard, the non-steroidal compounds of the present invention act as E1-STS inhibitors.

Another advantage is that the compounds may not be capable of being metabolised to compounds which display or induce hormonal activity.

The preferred compounds of the present invention are further advantageous in that the sulphamate compounds have an irreversible inhibitory effect.

Preferred compounds of the present invention are further advantageous in that they may also inhibit DHEA-STS.

Thus, in a preferred embodiment, the non-steroidal compounds are useful for the treatment of breast cancer. In addition, the non-steroidal compounds are useful for the treatment of non-malignant conditions, such as the prevention of auto-immune diseases or the improvement of long or short term memory, particularly when pharmaceuticals may need to be administered from an early age.

A particularly preferred non-steroidal compound according to the present invention is 4-0-sulphamoyl nonophenone, or a derivative with a nitro or cyano substituent.

A highly preferred embodiment of the present invention therefore relates to pharmaceutical composition comprising 4-O-sulphamoyl nonophenone or a said derivative and a pharmaceutically acceptable carrier, excipient or diluent.

The present invention therefore relates to non-steroidal compounds which are suitable for use as sulphatase inhibitors.

Of the preferred compounds, 4-O-sulfamoyl nonaphenone together with 4-O-sulfamoyl octaphenone appear particularly active *in vitro*. In this regard, 4-O-sulfamoyl nonophenone inhibited placental microsomal oestrone sulphatase by 76.4% at 5μM with an IC_{50}, of 0.86μM. 4-O-sulfamoyl octophenone also inhibited placental microsomal oestrone sulphatase by 80.1% at 5μM with an IC_{50}, of 1.16μM. This inactivation was shown to be in a similar way to EMATE which inhibited placental microsomal oestrone sulphatase with an IC_{50}, of 0.11μM

The non-steroidal compounds of the present invention, in particular the preferred nitrated and non-nitrated sulphamates, represent important compounds for the optimisation of non-steroidal sulphatase inhibition. The compounds are also believed to have therapeutic uses other than for the treatment of endocrine-dependent cancers, such as the treatment of autoimmune diseases. The compounds may also have uses in the increasing of short (and long) term memory .

Aspects of the present invention will now be described further by way of example with reference to the accompanying drawings.

Brief Description of Drawings

Figure 1 shows the known structures of oestrone (1), oestrone sulphate (2), EMATE (3) and COUMATE (4);

Figure 2 Shows the structures of 4-O-sulfamoyl benzaldehyde (11), 4-O-sulfamoyl benzophenone (12), 4-O-sulfamoyl acetophenone (13), 4-O-sulfamoyl propiophenone (14), 4-O-sulfamoyl octophenone (15) and 4-O-sulfamoyl nonophenone (16);

Figure 3 is a reaction scheme for the sulphamoylation of 4-hydroxy nonophenone; and

Figure 4 a, b and c are dose-response curves showing plots of percentage inhibition versus Log [I] for the inhibition of placental microsomal oestrone sulphatase by compounds 13, 15 and 16 embodying the invention.

Modes for Carrying Out the Invention

EXAMPLES

General Procedure for the Synthesis of hydroxyalkylphenones

Aluminium chloride (2 moles equivalent) was added to a stirred solution of phenol in dichloromethane at 0°C

under an atmosphere of nitrogen for 0.5 hours. The appropriate acid chloride (1.1 moles equivalent) was then added dropwise, and the reaction allowed to warm up to ambient temperature overnight. The slurry was then cautiously diluted with cool 1M HCl (30ml), and extracted into ether (3 x 30ml). The combined ether layers were extracted with 2M NaOH (3 x 30ml). The combined aqueous layers were acidified to pH 2 with 1M HCl, and extracted into ether (3 x 75ml). The organic layers were combined and washed with saturated $NaHCO_3$ (3 x 20ml), and water (2 x 50ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give residues which were either crystallised in hexane, or columned (50 ether:50 petroleum spirits 60-40°C) to give the required hydroxylalkylphenones.

Amino sulfonyl chloride (4) :

Methanoic acid (1.00mL, 26.50mmol) was added drop wise to chlorosulfonyl isocyanate (2.31ml, 26.50mmol, dried over B_2O_3), under nitrogen at 0-4°C. After evolution of gas, anhydrous toluene (20ml) was added to dissolve the product, and the solution stirred for 1 hour . Insoluble by products were removed by filtration. Removal of toluene under vacuum (<30°C) gave (4) as a yellow/orange solid, m.p. 33-38°C (expected 40°C Appel & Berger); R_f = 0.93 compared to chlorosulfonyl isocyanate R_f= 0.15 [DCM].

4-O-Sulfamoyl benzene (5) :

NaH (80% dispersion in mineral oil, 0. 12g, 4.00mmol) was added to a stirred solution of phenol (0.30g, 3.19mmol) in DMF (20ml) under nitrogen at 0°C. After evolution of hydrogen had ceased, aminosulfonyl chloride in toluene (10ml, ~10mmol) was added in one portion and the reaction allowed to stir overnight. The reaction was then quenched in $NaHCO_3$ (50ml), extracted into DCM (2 x 50ml), washed (3 x 30ml water) and dried ($MgSO_4$). Removal of the solvent under vacuum yielded a yellow oil, which was run through a column to give (5) (0.14g, 25.4%) as a pure white solid m.p. 77.6-81.2°C. R_f= 0.32 [diethyl ether / petroleum ether 40-60°C (6: 4)].

$\nu_{(max.)}$ (Film) cm^{-1} : 3421.1 and 3307.8 (NH), 1367.5 and 1177.2 (S=O). 300MHz δ_H ($CDCl_3$) 7.43-7.25 ($5H_2$ m, ArH), 5.24 (2H, s, NH_2). δ_C *($CDCI_3$)* 150.024, 129.923, 127.306, 122.142. MS (M^+) calculated mass 173.014665, actual mass 173.015633.

4-O-Sulfamoyl benzophenone (12)

Compound (12) was synthesized following the same procedures as for compound (5) except that NaH (80% dispersion in mineral oil, 0.10g, 3.33mmol) was added to a stirred solution of 4-hydroxybenzophenone (0.48g, 2.42mmol) in DMF (10ml). Aminosulfonyl chloride in toluene (10ml, ~10mmol) was added after 30min. Removal of the solvent under vacuum yielded an orange oil, which was

run through a column to give (12) (0.24g 35.8%) as a pure white solid m.p. 139.5-142.4°C. R_f= 0.34 [ethyl acetate / petroleum ether 40-60°C (3.5 : 6.5)].

$\nu_{(max)}$ (Film) cm^{-1} : 3336.7cm^{-1} (NH), 1631.4cm^{-1} (C=O), 1378.0 and 1178.5 (S=O). 300MHz δ_H ($CDCl_3$) 7.89-7.4;3 (9H, m, ArH), 5.12 (2H, s, NH2). MS m/z 277 (M^+), 121 (base peak).

4-O-Sulfamoyl acetophenone (13).

Compound (13) was synthesized following the same procedures as for compound (5) except that NaH (80% dispersion in mineral oil, 0.18g, 6.00mmol) was added to a stirred solution of 4-hydroxyacetophenone (0.50g, 3.66mmol) in DMF (10ml). Aminosulfonyl chloride in toluene (10ml, ~10mmol) was added after 30 minutes. Removal of the solvent under vacuum yielded an orange oil, which was run through a column to give (13) (0.05g, 6.3%) as a pure white solid R_f= 0.21 [ethyl acetate / petroleum ether 40-60°C (3.5 : 6.5)].

$\nu_{(max)}$ (Film) cm^{-1} : 3388.2cm^{-1} (NH), 1664.2cm^{-1} (C=O), 1377.8 and 1177.0cm^{-1} (S=O). 300MHz δ_H ($CDCl_3$) 8.04-8.01 (2H, dd, J = 9Hz, ArH), 7.44-7.41 (2H, dd, J = 9Hz, ArH), 5.10 (2H, s, NH_2), 2.62 (3H, s, H_3C-).

4-O-Sulfamoyl propiophenone (14)

Compound (14) was synthesized following the same procedures as for compound (5) except that NaH (80%

dispersion in mineral oil, 0.18g, 6.00mmol) was added to a stirred solution of 4-hydroxypropiophenone (0.50g 3.33mmol) in DMF (10ml). Aminosulfonyl chloride in toluene (10ml, ~10mmol) was added after 30 min. Removal of the solvent under vacuum yielded an orange oil, which was run through a column to give (14) (0.09g, 11.8%) as a pure white solid m.p. 105.8-106.7°C. R_f= 0.30 [ethyl acetate / petroleum ether 40-60°C (3.5 : 6.5)].

$\nu_{(max)}$ (Film) cm^{-1} : 3388.6cm^{-1} (NH), 1677.0cm^{-1} (C=O), 1370.2 and 1181.2cm^{-1} (S=O). 300MHz δ_H ($CDCl_3$) 8.03-8.00 (2H, dd, J = 9Hz, ArH), 7.42-7.40 (2H, dd, J = 9Hz, ArH), 5.14 (2H, s, NH_2), 3.03-2.96 (2H, q, J=7Hz, $C\underline{H}_2CH3$) 1.25-1.20 (3H, t, J= 7Hz, $CH_2C\underline{H}_3$).

4-O-Sulfamoyl octanophenone (15)

Compound (15) was synthesized following the same procedures as for compound (5) except that NaH (60% dispersion in mineral oil, 0.10g, 2.50 mmol) was added to a stirred solution of 4-hydroxyoctanophenone (0.50g 2.27mmol) in DMF (10ml). Aminosulfonyl chloride in toluene (10ml, ~10mmol) was added after 30 min. Removal of the solvent under vacuum yielded an orange oil, which was run through a column to give (15) (0.25g 36.8%) as a pure white solid m.p. 105-107°C. R_f= 0.46 [ether / petroleum ether 40-60°C (7 : 3)].

$\nu_{(max.)}$ (Film) cm^{-1} : 3389.1cm^{-1} (NH), 1681.8cm^{-1} (C=O), 1377.5 and 1181.1cm^{-1} (S=O). 300MHz δ_H ($CDCl_3$) 8.02-7.98

(2H, dd, J = 9Hz, ArH), 7.42-7.39 (2H, dd, J = 9Hz, ArH), 5.22 (2H, s, NH_2), 2.96-2.91 (2H, t, J=7Hz, $COC\underline{H_2}CH_2$), 1.75-1.67 (2H, m, J = 7Hz, $COCH_2\underline{CH_2}CH_2$), 1.40-1.29 (8H, m, $COCH_2CH_2[\underline{CH_2}]_4CH_3$ 0.90-0.86 (3H, t, J = 7Hz, CH_3).

4-O-Sulfamoyl nonanophenone (16)

Compound (16) was synthesized following the same procedures as for compound (5) except that NaH (60% dispersion in mineral oil, 0.18g, 4.50mmol) was added to a stirred solution of 4-hydroxynonanophenone (1.0g, 4.27mmol) in DMF (10ml). Aminosulfonyl chloride in toluene (10ml, ~10mmol) was added after 30 min. Removal of the solvent under vacuum yielded a clear oil, which was run through a column to give (16) (0.29g 21.7%) as a pure white solid m.p. 102-104°C. R_f = 0.57 [ether / petroleum ether 40-60°C (7 : 3)].

$\nu_{(max.)}$ (Film) cm^{-1} : 3389.0 and 3289.0cm^{-1} (NH), 1682.3cm^{-1} (C=O), 1377.9 and 1181.8cm^{-1} (S=O). 300MHz δ_H ($CDCl_3$) 8.02- 7.99 (2H, dd, 1 = 9Hz, ArH), 7.42- 7.39 (2H, dd, J = 9Hz, ArH), 5.17 (2H, s, NH_2), 2.96-2.91 (2H, t, 1=7Hz, $COC\underline{H_2}CH_2$), 1.74-1.69 (2H, m, J = 7Hz, $COCH_2\underline{CH_2}CH_2$), 1.40-1.29 (10H, m, $COCH_2CH_2[CH_2]CH_3$ 0.90-0.86 (3H, t, J = 7Hz, CH_3). MS m/z313 (M^+), 121 (base peak)

***In vitro* biological testing**

The total assay volume was 1ml. ^{3}H-estrone sulfate (25μl, 20μM/tube; 300,000dpm/tube) and the inhibitors

(25μl in various concentrations) dissolved in ethanol were added to a 10ml assay tube, and the ethanol removed with a stream of nitrogen. Tris-HCl buffer (0.05M, pH7.2, 0.2ml) was added to each tube. Placental microsomes were then diluted with Tris-HCl buffer (115μg/ml). The microsomes and assay tubes were preincubated for 5min at 37°C in a shaking water bath prior to the addition of the microsomes (0.8ml) to the tubes. After 20 min incubation (at 37°C), toluene (4ml) was added to quench the assay, and the tubes placed in ice. The quenched samples were vortexed for 45 s and centrifuged (3000 rpm, 10 min). 1ml of toluene was added to 5ml scintillation cocktail (TRITON-X). The aliquots were counted for 3min. All samples were run in triplicate. Control samples with no inhibitor were incubated simultaneously. Blank samples were obtained by incubating with boiled microsomes.

Table I presents data for compounds 13, 14, 15, 16 of the invention and also for the known compounds EMATE and COUMATE. Figs. 4a, b and c present the data for compounds 13, 15 and 16 graphically.

Table I: Assay Results

Compound	Inhibition Data			IC_{50} (μm/Tube)
	Conc. (μM/Tube)	Log Conc. (μM/Tube)	% Inhibition	
EMATE	0.01	-2	16.4	0.11

COUMATE	1	0	11.8	12.5
13	10	1	6.6	67.3
14	1	0	6.3	18.1
15	0.1	-1	14.8	1.16
16	0.1	-1	13.4	0.86

We have also prepared a series of simple model compounds of formula Y-Ph-O.SO_2.NH_2 by treating the corresponding phenols Y-Ph-OH with H_2NSO_2Cl and base (NaH or K_2CO_3) in toluene and have measured (i) the pK_a values of the phenols; and (b) the IC_{50} values of the sulphamates, using the assay described above. The results are presented in Table II below. These show the relationship between pK_a of the phenol and inhibitory activity of the sulphamate which also holds good for the compounds of the present invention.

Table II: Relationship of pK_a and IC_{50} for Y-Ph-OSO_2NH_2

Group Y	Substitution	pK_a	$IC_{50}/\mu M$
CH_3	3	10	>10,000
F	3	9.16	2089
Cl	3	9	537
Br	3	8.95	257
CN	3	8.54	190.5
NO_2	3	8.28	120
CH_3	4	10.2	>10,000

F	4	9.8	>10,000
Cl	4	9.5	1584.8
Br	4	9.29	912
CN	4	8.02	300
NO_2	4	7.15	330

As the pK_a falls from a high value, the activity of the sulphamate rises to a maximum, and then begins to fall again. The optimum pK_a range is around 7-9, preferably 7-8 or 7.5-8.5. Such a relationship also applies with the compounds of the invention such as those shown in Fig. 2. Thus it will generally be the case that inclusion of a strongly electron-withdrawing substituent such as NO_2 or CN (particularly o or p to the sulphamate group) will produce a significant increase in activity. Adding a second such substituent will generally not have a comparable effect, unless there is also a strongly electron donating substituent.

The compounds of the invention exemplified above (Table I) are simpler compounds than EMATE and COUMATE but have comparable inhibitory activities, without side effects due to oestrogenic activity. Inclusion of electron withdrawing substituents will further enhance the desirable properties.

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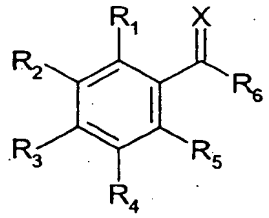
CLAIMS:

1. A compound of formula (A) or a salt thereof:



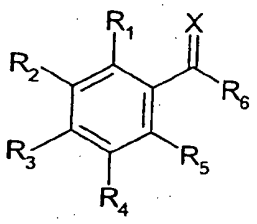
(A)

wherein R_1-R_5 are independently selected from H, halo, alkyl, nitro, CN, aryl, OH, OR' (where R' is alkyl or aryl), $NR"_2$ (where each R" is independently H, alkyl or aryl) and sulphamate groups, with the proviso that at least one of them is a sulphamate group; X is selected from O, S, NH, NR''' where R''' is alkyl or aryl), and R_6 is selected from H, alkyl, aryl, alkoxy, aryloxy and $NR"_2$.

2. A compound according to claim 1 wherein the groups R_1-R_5 and R_6-C(=X)- are selected so as to have an overall electron-withdrawing effect on the benzene ring to which they are attached.

3. A compound according to claim 1 or claim 2 which is a sulphamate of a phenol having a pK_a in the range 7-9.

4. A compound of formula (A) or a salt thereof



(A)

wherein X and R_6 are as defined in claim 1, and one of R_1-R_5 is a sulphamate group and the others are selected so that the compound is a sulphamate ester of a phenol having a pK_a in the range 7-9.

5. A compound according to any preceding claim wherein R_3 is a sulphamate group.

6. A compound according to claim 5 wherein three of R_1, R_2, R_4 and R_5 are H and the fourth is selected from H and electron withdrawing groups.

7. A compound according to any preceding claim wherein X is O.

8. A compound according to any preceding claim wherein R_6 is H or a hydrocarbyl group selected from C_{1-8} alkyl and phenyl.

9. A method of preparing a compound according to any preceding claim comprising reacting a phenol with a sulphamoylating agent to convert it into a sulphamoyl

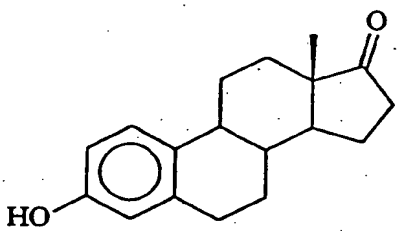
benzene.

10. A pharmaceutical composition comprising a compound of any of claims 1-8.

11. Use of a compound of any of claims 1-8 in the manufacture of a composition for use in the treatment or prophylaxis of a condition associated with a sulphatase.

12. Use according to claim 11 wherein the sulphatase is oestrone sulphatase and/or dehydroepiandrosterone sulphatase.

13. Use according to claim 11 or 12 wherein the condition is an endocrine-dependent cancer.



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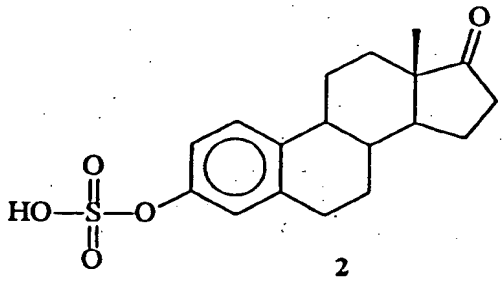

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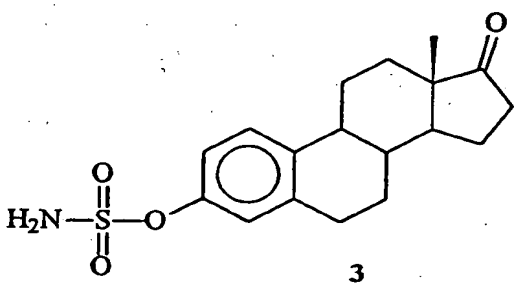
Fig. 1



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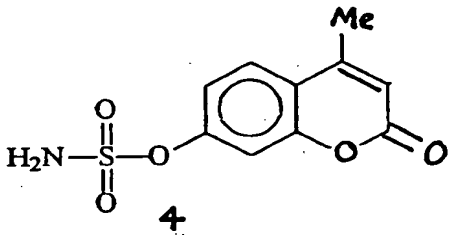

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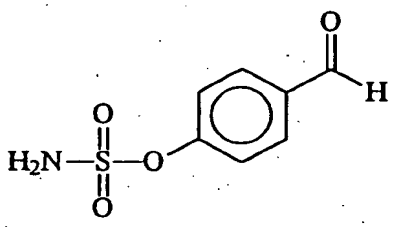

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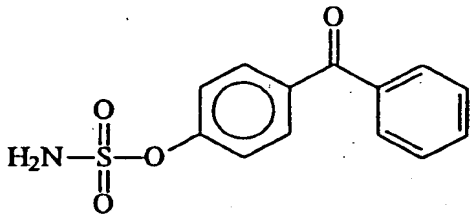

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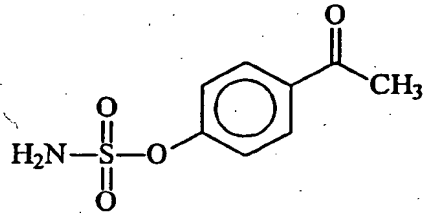

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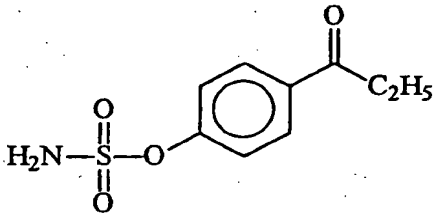

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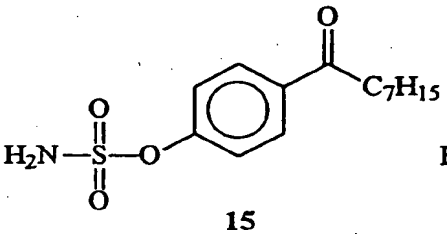

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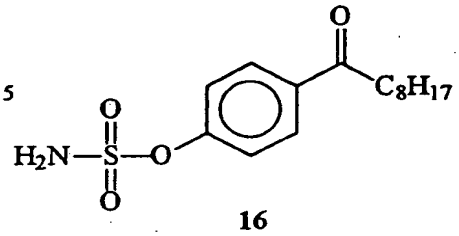

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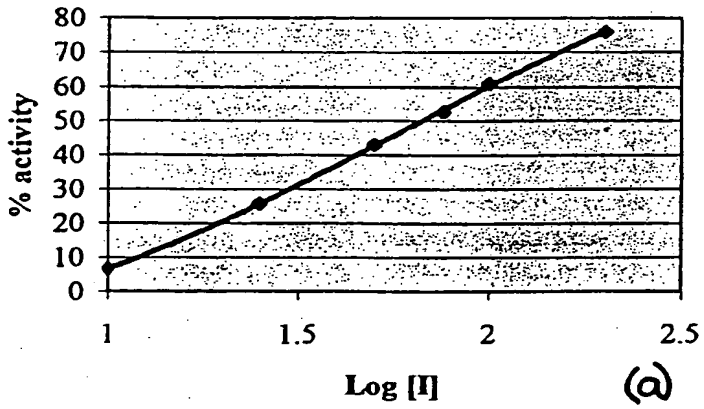
Fig. 2

Fig 4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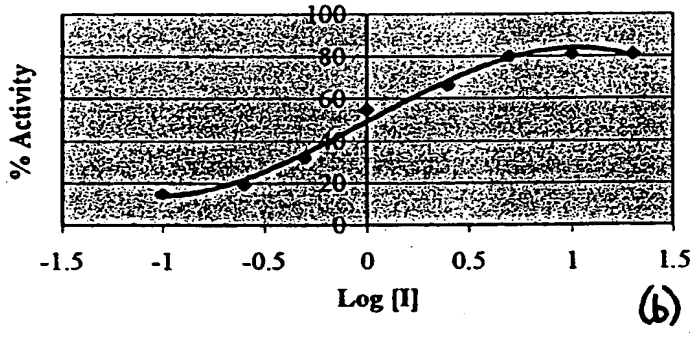
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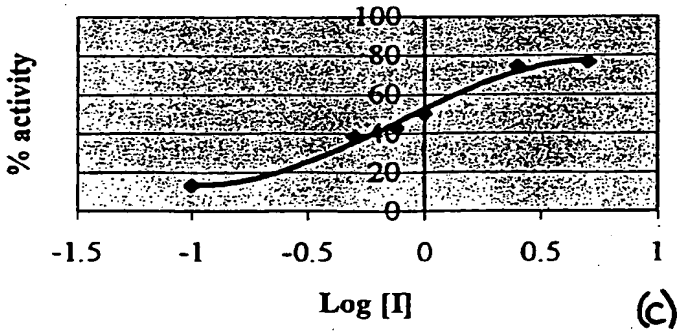
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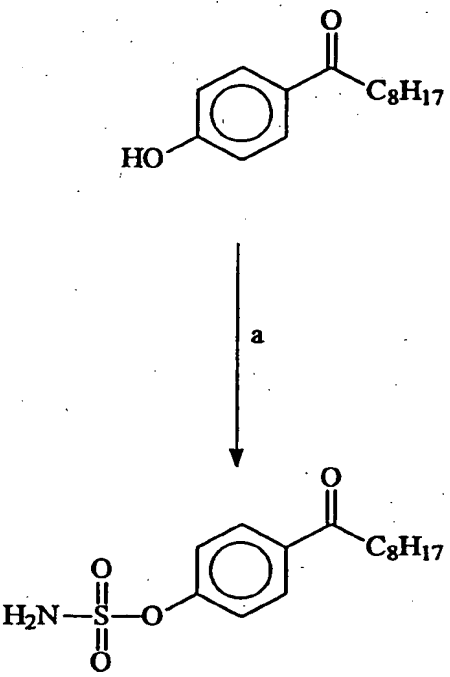
Fig 3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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 00/02592

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C307/02 A61K31/095

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN-INFORMATION SERVIVE; FILE: REGISTRY, XP002148810 see RN: 1999984-64-0 & WO 97 44314 A (WARNER-LAMBERT OMPANY) 27 November 1997 (1997-11-27) ---	1
X	KAMAL: "Cyclization of ..." J. ORG. CHEM., vol. 53, 1988, pages 4112-4114, XP000940769 see formula 5: compounds 5a-5h ---	1
A	WO 97 32872 A (IMPERIAL COLLEGE ;UNIV BATH (GB); REED MICHAEL JOHN (GB); POTTER B) 12 September 1997 (1997-09-12) the whole document ---	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 September 2000	25/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 567 831 A (LI PUI-KAI) 22 October 1996 (1996-10-22) the whole document	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9732872 A	12-09-1997	AU 2225597 A	22-09-1997
		EP 0885211 A	23-12-1998
		JP 2000506161 T	23-05-2000
		US 6083978 A	04-07-2000
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		DE 69608904 D	20-07-2000
		EP 0845985 A	10-06-1998
		JP 11510813 T	21-09-1999
		WO 9706793 A	27-02-1997

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